Coagulation factor IX

**Indication**
Coagulation defects, purpura or other haemorrhagic or related conditions

**ICD11 code:** 3B6Z

**Medicine type**
Biological agent

**List type**
Complementary (EML) (EMLc)

**Additional notes**
All human plasma-derived medicines should comply with WHO requirements.

**Formulations**
Parenteral > General injections > IV: 500 IU in vial powder for injection; 1000 IU in vial powder for injection

**EML status history**
- First added in 1979 (TRS 641)
- Changed in 1989 (TRS 796)
- Changed in 2007 (TRS 950)
- Changed in 2013 (TRS 985)
- Changed in 2021 (TRS 1035)
- Changed in 2023 (TRS 1049)

**Sex**
All

**Age**
Also recommended for children

**Therapeutic alternatives**
coagulation factor IX complex

**Patent information**
Read more about patents.

**Tags**
Biological

**Wikipedia**
Coagulation factor IX

**DrugBank**
Coagulation factor ix, ii, vii, x (Factor IX Complex (Human))

**Expert Committee recommendation**

The Expert Committee recalled the recommendation of the 2021 Committee that the square box listings for blood-derived coagulation factors VIII and IX be reviewed in 2023, such that the listings should explicitly indicate the recommended therapeutic alternatives. The application from the World Federation of Hemophilia proposed therapeutic alternatives to coagulation factor VIII (recombinant factor VIII, bypassing agents, bispecific monoclonal antibody factor VIII mimic and desmopressin) and coagulation factor IX (recombinant factor IX, coagulation factor IX complex and bypassing agents), but did not provide a comprehensive review of the evidence supporting these suggestions. In consideration of the application, the Committee made the following comments and recommendations. Recombinant coagulation factors. The Committee noted that when plasma-derived coagulation factors were considered for inclusion on the first EMLc in 2007, the Committee at that time considered that recombinant products would be covered by the existing square box listings. However, a comprehensive review of the evidence for the comparative efficacy, safety and cost/cost–effectiveness of recombinant products had not been conducted nor evaluated at that time. The 2023 Committee therefore recommended that a full application, compliant with EML application requirements, be requested so that the available evidence could be evaluated. Until such time, recombinant coagulation factors should not be included as therapeutic alternatives to plasma-derived coagulation factors on the Model Lists. Bypassing agents The Committee considered that bypassing agents were not, as such, therapeutic alternatives to coagulation factors, but rather were currently used in a subset of patients who develop factor VIII or factor IX alloantibodies (inhibitors). With regard to the bispecific monoclonal antibody, emicizumab, the Committee...
also considered that this was not as such, a therapeutic alternative to factor VIII, but rather could be used as a separate treatment strategy for patients with haemophilia A. Therefore, the Committee recommended that these therapies not be included as alternatives under the current square box listings. The Committee acknowledged the potential future role of these therapies in changing the treatment paradigm of patients with haemophilia but also noted that currently they may not be considered as cost-effective, nor are they widely available. The Committee considered that high-quality applications, compliant with EML application requirements for these therapies could be considered for independent inclusion in the Model Lists in the future. Desmopressin

The Committee acknowledged that desmopressin was a therapeutic alternative to plasma-derived factor VIII. Desmopressin is already included on the EML and EMLc for use in the treatment of patients with haemophilia A and von Willebrand disease, in Section 10 (Medicines affecting the blood), instead of as a square box alternative to factor VIII in Section 11 (Blood products of human origin and plasma substitutes) since it is not a blood product of human origin. Coagulation factor IX complex

The Committee noted that this complex had been previously listed on the Model Lists until 2013, when it was replaced by coagulation factor IX when Section 11 of the lists for blood products of human origin and plasma substitutes was revised and restructured. The Committee considered that coagulation factor IX complex could be considered a suitable therapeutic alternative to coagulation factor IX in situations where purified factor IX was not available. Therefore, the Committee recommended that the square box listing for coagulation factor IX specify coagulation factor IX complex as a therapeutic alternative under such circumstances.

Dextran

In response to the suggestion in the application to remove the plasma substitute dextran from the Model Lists because it is not used in the treatment of haemophilia, the Committee advised that dextran was still an essential plasma substitute for other patients in need of blood volume replacement and therefore should remain listed.

Strengths of factor VIII and factor IX

The application proposed the removal of the specification of strengths of factor VIII and factor IX from the listings, because factor VIII and IX concentrates are manufactured and supplied in strengths ranging from 250 IU to 4000 IU per vial. The Committee agreed that specifying a single strength vial could be unnecessarily limiting. The Committee recommended that for factor VIII, additional strengths of 250 IU and 1000 IU be included as these are the most commonly used and available. The Committee considered that the existing listed strengths of factor IX were appropriate and therefore did not recommend inclusion of the other strengths proposed.

Plasma-derived coagulation factors VIII and IX are each listed on the EML and EMLc with a square box, which is intended to indicate similar clinical performance of different medicines within the pharmacological class and that suitable therapeutic alternative may be considered for selection at the country level for national essential medicines lists. The square box was originally added to the listings in 1989 to accommodate cryoprecipitate as a therapeutic alternative to factor VIII, and plasma and cryoprecipitate-poor plasma as therapeutic alternatives to factor IX (1). In 2007, when plasma-derived coagulation factors VIII and IX were included on the first EMLc, the Expert Committee recognized that recombinant products should be used in preference to dried and plasma-derived products and that recombinant products would be captured by the square box listings (2). At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for plasma-derived coagulation factors VIII and IX be reviewed and updated in 2023 (3). Thus, the Secretariat invited the World Federation of Hemophilia to submit an application reviewing the therapeutic alternatives for these medicines.

The public health relevance of coagulation factors for use in the treatment of haemophilia is well established.

The application proposed a series of changes to listings as summarized below. Coagulation factor VIII

The World Federation of Hemophilia recommended not specifying the 500 IU strength with the listing for coagulation factor VIII as this could be unnecessarily limiting. This is because factor VIII concentrates are manufactured in a variety of vial sizes, labelled with strengths ranging from 250 to 3000 IU per vial. The administered dose is determined by the respective treatment protocol and patient weight. The Federation recommended the inclusion of recombinant factor VIII as a therapeutic alternative based on: human-derived and recombinant factor VII products being classified with the same Anatomical Therapeutic Chemical (ATC) code (B02BD02); the recognition by the Expert Committee in 2007 that recombinant products should be used in preference to plasma-
Harms

A comprehensive review of the available evidence for safety was not provided in the application.

Cost / cost effectiveness

No information was provided in the application.

WHO guidelines

WHO guidelines for the treatment of haemophilia are not currently available. The WHO Expert Committee on Biological Standardization has developed requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (5), guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood products (6), and guidelines on management of blood and blood components as essential medicines (7).
No information was provided in the application.


